IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appl. No.	:	10/788,489	Confirmation No. 9027
Applicant	:	Serge CARILLO, et al.	
Filed	:	March 1, 2004	
TC/A.U.	:	1633	
Examiner	:	Scott Long	
Title	:	METHOD OF CANCER TREATMENT BY P53 PROTEIN CONTROL	
Docket No.	:	ST94037A/80375.0033	
Customer No.	:	29693	

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
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APPLICANTS' BRIEF ON APPEAL

Sir:

This is an appeal from the Final Office Action dated July 10, 2009 ("the Final Office action"). A Notice of Appeal was timely filed on November 30, 2009.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal are the inventors and sanofi-aventis, the successor to employer of each of the inventors, to whom the inventors had an obligation of assignment.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants, Appellants' representatives, or the real parties in interest that will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

Claims 1-8 are pending. The Claims Appendix includes a listing of the claims involved in the appeal as they presently stand.

IV. STATUS OF THE AMENDMENTS

Applicants have not submitted an amendment after the filing of the Notice of Appeal. All previously-submitted amendments have been entered.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Generally, the claims relate to a method for detecting an inhibitor of p53 protein degradation. Claim 1 recites a method involving a cell extract containing one or more p53 proteins and one or more proteases, and administering a peptide or protein inhibitor of calpain protease activity to the cell extract, and measuring p53 protein and p53 protein fragments (specification at page 8, lines 10-26; Example 1 at page 19, line23 to page 21, line 3; Example 2 at page 21, line 5; and page 5, lines 6-21). Claim 2 involves the inhibitor calpastatin (specification at page 23, lines 12-23; page 5, lines 20-21). Claim 3 refers to a calpastatin of SEQ ID No: 1-3 (specification at page 5, lines 3-4; page 7, lines 13-20). Claim 4 refers to a cell extract derived from a tumor cell (specification at page 21, lines 18-20; page 5, line 25 to page 6, line2). Claim 5 refers to a method where the inhibitor administered is a fragment of calpastatin (specification at page 6, lines 2-9). Claim 6 refers to the method of claim 4 where the inhibitor is calpastatin (specification at page 5, lines 20-22). Claim 7 refers to a method of claim 4 where the inhibitor is a fragment of calpastatin (specification at page 6, lines 2-9). And claim 8 recites a method where measuring the p53 protein and p53 protein fragments is performed using gel electrophoresis (specification at Figure 1, described at page 17, lines 18-26; page 23, lines 20-27).

Claims 3, 5, and 7 are separately patentable as they recite a calpastatin fragment used to inhibit p53 degradation.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Final Office Action includes one new rejection of all the claims under 35 U.S.C. § 103(a). As explained in the Final Office Action at pages 4-5, this rejection is based upon the combination of "Ramsby et al. (Electrophoresis 15(2): 265-277), and further in view of Robaye et al. (Electrophoresis 15: 503-510), and further in view of Squier et al. (Journal of Cellular Physiology 159(2): 229-237), and further in view of Lowe et al. (Nature 362: 847-849), and further in view of Lane et al (British Medical Bulletin 50(3): 582-599)."

All other rejections have been withdrawn.

VII. ARGUMENT

The basis for the rejection, as expressed in the Final Office Action and the comments in the Advisory Action of October 30, 2009, repeatedly refers to methods for detecting inhibitors of proteolysis. The claimed invention is not so general and instead recites a method of detecting "p53 protein degradation" (*see* claim 1). The specification indicates that the invention derives at least in part from the knowledge that p53 protein is "degraded specifically by m-calpain or u-calpain," knowledge one of skill in the art did not have at the time of filing. Specification at page 3, line 26 to page 4, line 8. Without some actual motivation to use a peptide or a protein as an inhibitor of calpain for the purpose of detecting this specific p53 degradation, as claimed in claim 1, the cited references and combinations of them can only refer to a general search for protease inhibitors that may relate to apoptosis This is not a sufficient reason for one to arrive at the claimed invention.

Furthermore, while Applicants have asked for specific language from the cited documents that allegedly teach "administering a peptide or protein inhibitor of calpain protease activity," no such language was mentioned in the Advisory Action. Instead, the comments from the Advisory Action rely on either the knowledge that protein inhibitors of calpain exist or the "indirect" use of peptide or protein inhibitors, apparently from the EDTA chemical compound noted in Ramsby. Advisory Action at page 2. Clearly, one of ordinary skill in the art knows that EDTA is not a peptide and is not a protein.

A. At the time of filing, the person of ordinary skill in the art did not have knowledge of peptide or protein compounds to specifically inhibit p53 degradation.

Prior art references need not teach or suggest each and every limitation of a claim for that claim to be obvious. However, and especially in this case, Applicants contend that the differences between the claimed invention and the multiple references cited are sufficiently great so as to render the claimed invention non-obvious to one of ordinary skill in the art at the time the invention was made. See, for example, M.P.E.P. § 2141(II) ("In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge."). In particular, as discussed in further detail below, Applicants contend that the cited references, even in combination, fail to teach or suggest a p53 protein degradation method and at least the step of claim 1 reciting "administering a peptide or protein inhibitor of calpain protease activity to the cell extract."

The Examiner has repeatedly relied on Ramsby. Nevertheless, Ramsby explicitly teaches that EDTA (the alleged calpain inhibitor) is added to digitonin and Triton buffers, and not to a cell extract containing p53 and a protease. Ramsby, p. 268, col. 1, ll. 47-50 ("The addition of EDTA to digitonin and Triton buffers enhances the rate and selectivity of fractionation and prevents undesirable degradation of cellular proteins by calcium-activated proteases"). Significantly, the Examiner explicitly concedes that

"Ramsby et al. do not specifically teach administering protein inhibitors of calpain to the cell extract." Final Office Action at page 7.

The allegation in the Advisory Action that Ramsby "indirectly" teaches a step of administering a "calpain inhibitor" merely re-states the differences between the EDTA used by Ramsby, a commonly used, non-specific protease inhibitor and detergent, and the claimed invention reciting peptide inhibitors or protein inhibitors. Clearly, these are very different classes of compounds. The use of a detergent aids in the separation of cell components, which is the focus of the fractionation work in Ramsby. While methods to detect **a protein** or **a peptide** that can inhibit the calpain degradation of p53, as claimed, relate directly to the cellular processes one of skill in the art knows p53 is involved in. Applicants' specification is the lone source of information connecting the inhibition of p53 degradation to the specific calpastatin protein and the specific peptide fragments of calpastatin as recited in the claims. Indeed, the Examiner concedes that "none of the above references specifically indicate that p53 is a substrate of calpain." Final Office Action at page 8.

None of the remaining references compensate for this deficiency.

In particular, The Examiner explicitly concedes that "Robaye et al. have not treated the cell extracts with particular proteolysis inhibitors of calpain." Final Office Action at page 7.

Squier merely mentions calpastatin in the context of explaining potential reasons for changes in the activity of calpain. Of course, this has no connection whatsoever to p53 degradation. Squier does not disclose administration of calpastatin or any other

peptide or protein inhibitor of calpain protease activity to a cell extract containing p53 as claimed. See Squier, p. 235, col. 1, ll. 4-6.

Lane and Lowe do not mention calpain or calpastatin.

Accordingly, Applicants respectfully submit that no reason in logic or based upon the actual contents of the cited documents leads one of ordinary skill in the art to a method for detecting p53 degradation by "administering a peptide or protein inhibitor of calpain protease activity to the cell extract."

B. The multiple references that teach away should be read fairly and the basis for why the teaching away leads one on a divergent path from the invention should be fully considered.

As noted in the M.P.E.P. at § 2141.02, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." Also, "[a] 'reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.'" *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). As detailed below, each of Squier, Robaye, and Lane teach away from the claimed invention.

Both Robaye and Squier teach away from the combination with Ramsby, Lowe, and Lane as asserted here. The Federal Circuit has explicitly stressed that "as a useful general rule … references that teach away cannot serve to create a prima facie case of

obviousness." *McGinley v. Franklin Sports, Inc.,* 262 F.3d, 1339, 1354 (Fed. Cir. 2001), citing *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). In this case, Applicants have shown that Squier states that "[p]reincubation with calpain inhibitors **prevented** apoptosis in thymocytes whether induced by dexamethasone or by low-level irradiation," and that "calpain is necessary for triggering apoptosis." Squier, col. 2, ll. 25-26 (emphasis added). This relates to the opposite of what is discussed in the specification at page 2, where p53 protein "is capable of inducing apoptosis."

One of skill in the art would understand that if the calpain of Squier is **present** to degrade p53, then, logically, **p53 cannot induce apoptosis** as explained in Applicants' specification at page 2, lines 14-20, and acknowledged by the Examiner. But calpain, according to Squier, is necessary for apoptosis. There is no explanation for this confusion or discrepancy between Squier and the teachings of the specification and the claims of the invention. One of skill in the art would understand that the claimed methods refer to the inhibition of p53 degradation, which would result in p53-induced apoptosis. Clearly, this is the opposite of what Squier discusses.

Furthermore, Squier refers to the importance of "pre-incubation" with calpain inhibitors for the work focusing on dexamethasane-induced changes. This is at best a confusing experiment with respect to its direct implications on the claimed invention and more correctly a divergent approach for detecting apoptosis, but not inhibitors of p53 degradation.

The Robaye document states that "a role for proteolysis in apoptosis is supported by evidence of increased protease activity during apoptotic regression and by **the ability of protease inhibitors to block apoptosis** in some cases." Robaye, p. 503,

col. 2, lines 6-10 (emphasis added). Again, this statement seems completely at odds with the purposes of Applicants' invention. Indeed, one of the objects of Applicants' invention is to trigger apoptosis in tumor cells by using calpain inhibitors to prevent calpain degradation of wild-type p53. See specification at page 4, lines 9-25.

In fact, in view of the references cited by the Examiner, the skilled artisan would have absolutely no reason to combine p53 (mentioned briefly in Ramsby, Lowe, and Lane) with calpain and calpastatin (discussed in Robaye and Squier) if the artisan's goal was to trigger apoptosis in tumor cells. One of skill in the art understands the presence of p53 in cells triggers apoptosis. So, the steps of the claimed method are the opposite of what Robaye and Squier teach and suggest one to do. The combination with Robaye and Squier present a "seemingly inoperative" method, at least an expectation of inoperative results from the method derived from the combination, or more properly a divergent method. Accordingly, the combination of Ramsby with one or more of Robaye or Squier cannot serve as a basis for a *prima facie* case of obviousness. *McGinley v. Franklin Sports, Inc.,* 262 F.3d, 1339, 1354 (Fed. Cir. 2001),

In addition, Lane expressly teaches away from the claimed invention. Lane states that "the HPV E6 protein also acts to promote the rapid breakdown of p53 by specifically targeting its destruction through the ubiquitin pathway." Lane, p. 592, ll. 18-21. The ubiquitin pathway involves tagging substrates with ubiquitin and the destruction of the tagged proteins by the 26S proteasome. This is an entirely different pathway than the calpain degradation pathway described in Applicants' specification. Lane suggests that one of skill in the art look for a different protein degradation pathway and thus leads one away from p53 protein degradation. Thus, a person of skill in the art

would have not looked to Lane to arrive at the claimed invention, even if combined with the remaining references.

C. Viewed as a whole, the cited references do not support an obviousness conclusion or a reason to combine the teachings as alleged.

Applicants respectfully submit that if the cited references are viewed as a whole for what they mean to one of ordinary skill, no case of obviousness exists. By inappropriately focusing on the individual differences between the claimed invention and each reference, the Examiner has reached an incorrect conclusion. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." M.P.E.P. § 2141.02 (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983)). Moreover, the M.P.E.P. provides that "[a]scertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." M.P.E.P. § 2141.02.

The Ramsby reference, when viewed as a whole, demonstrates the nonobviousness of the present invention. Specifically, Ramsby discusses a method for "differential detergent fractionation (DDF) which reproducibly partitions hepatocytic proteins into four distinct fractions and appears to preserve cytoskeletal interactions." Ramsby, page 266, column 1, lines 48-52. The Examiner has provided no explanation as to why the skilled artisan would even consult this reference, or consider its teachings

remotely relevant to detecting an inhibitor of p53 protein degradation. Rather, the Examiner merely highlights the presence of terms common to the reference and to the claims at issue, without providing a detailed rationale as to why the reference as a whole should even enter the equation.

Similarly, while Robaye and Ramsby refer to gel electrophoresis, there is no suggestion to look for or detect specific inhibitors of p53 degradation using gel electrophoresis. The only motivation to use gel electrophoresis is supplied by Applicants' own teachings that p53 degradation can be specifically inhibited with peptide or protein inhibitors of calpain. Of course, this is improper hindsight analysis and cannot form the basis of a *prima facie* case.

VIII. CONCLUSION

Any method taught or suggested by the combination of Ramsby, Robaye, Squier, Lowe, and Lane fails to render the claimed invention obvious. Furthermore, claims 3, 5, and 7 reciting a fragment of calpastatin are separately patentable. None of the cited documents refer to or relate to any calpastatin fragments and their use as an inhibitor of calpain and p53 degradation.

Applicants respectfully request reversal of the rejection.

Appellant has also provided for the payment of the required fee for filing an appeal brief and for any extension of time required. If any fees are required or if any additional extension of time is necessary, Appellants hereby petition therefor under 37 C.F.R. § 1.136 and authorize payment from the undersigned's deposit account. Authorization is hereby granted to charge any fees due with the filing of this document, including fees for any extensions of time deemed necessary, to Deposit Account No. 50-1129 with reference to Attorney Docket No. 80375.0033.

Respectfully submitted,

WILEY REIN LLP

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CLAIMS APPENDIX

1. A method for detecting an inhibitor of p53 protein degradation comprising providing a cell extract containing one or more p53 proteins and one or more proteases, administering a peptide or protein inhibitor of calpain protease activity to the cell extract, and measuring p53 protein and p53 protein fragments.

2. The method of claim 1, wherein the inhibitor administered is a calpastatin.

3. The method of claim 2, wherein the calpastatin is encoded by one of SEQ ID NO: 1-3.

4. The method of claim 1, wherein the cell extract is derived from a tumor cell.

5. The method of claim 1, wherein the inhibitor administered is a fragment of calpastatin.

6. The method of claim 4, wherein the inhibitor is a calpastatin.

7. The method of claim 4, wherein the inhibitor is a fragment of calpastatin.

8. The method of claim 1, wherein measuring the p53 protein and p53 protein fragments is performed using gel electrophoresis.

EVIDENCE APPENDIX

NONE

RELATED PROCEEDINGS APPENDIX

NONE

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